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Designated Contracting States:
GB IE

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(56) References cited:

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WO-A-91/15594 **GB-A- 945 670**

- **SCIENCE, vol. 248, 1 June 1990, LANCASTER,**
PA., US., pages 1061-1062, XP000602095 C.
DJERASSI.: "Fertility awareness: Jet-age
rhythm method?"

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EP 0 745 854 B1

Description

[0001] This invention relates to methods and devices enabling contraceptive advice to be provided during the human ovulation cycle.

5 [0002] Devices are already commercially available which purport to provide the user with contraceptive advice. Generally these are based on the measurement of basal body temperature, and require the user to make daily measurements. The reliability of the contraceptive advice provided by such devices is questionable.

[0003] Devices are also available which measure the concentration of urinary luteinising hormone (LH), and alert the user to the LH surge indicative of ovulation, as an aid to conception.

10 [0004] Although the absolute urinary concentration value of LH varies from one individual to another, and from one cycle to another, the LH surge is such a pronounced event that for practical purposes a urinary LH concentration of 20mIU/ml can be regarded as a universal threshold indicative of the LH surge under virtually all circumstances.

[0005] Although the LH surge is a clearly measurable event, it has not hitherto been regarded as an acceptable indicator for contraceptive purposes because it occurs such a short while prior to actual ovulation. Practical contraceptive advice, which would allow a user to avoid conception by abstaining from unprotected intercourse (ie. without resort to any physical or hormonal contraceptive technique) for a minimal portion of the normal ovulation cycle, has not been considered possible if based solely on the measurement of urinary LH concentration.

[0006] The expression "LH surge" is used herein to mean the dramatic rise in LH concentration that precedes the event of ovulation. In the art, reference is made also to "LH max", i.e. the peak concentration of LH. In the majority of individuals, these are for all practical purposes simultaneous, when the cycle is monitored on a day-by-day basis. However, in a few individuals, perhaps 20% of the population, the actual peak concentration of LH is not observed until the day following the main concentration rise. For the purposes of the invention, we prefer to use the observable rise as the critical parameter.

[0007] By the invention we have found that, contrary to such expectation, reliable contraceptive advice can be derived simply from the measurement of urinary LH concentration if such measurement is linked to a critical 'calendar' provided for the user.

[0008] Previously proposed contraceptive methods based on urinary component analysis have tended to require extensive daily urine sampling and testing, often throughout the entire cycle. Other methods have tended to require an unduly prolonged period of abstinence from unprotected intercourse. The invention achieves a reasonable balance by enabling the testing period and abstinence period to be reduced while providing a worthwhile degree of certainty in the contraceptive advice to the user, and employs techniques that can readily be applied in the home.

[0009] The invention provides a method of reducing the likelihood of conception during the human ovulation cycle, wherein commencing on a predetermined day in the interval from numerical day 5 to numerical day 15 inclusive following the onset of menses, frequent (preferably daily) testing of urinary luteinising hormone (LH) concentration is performed until the LH surge associated with ovulation is detected, and unprotected intercourse is avoided during a time interval commencing on or before the first day of urinary LH concentration testing and ending at least 2 days, preferably at least 3 days, following the day of LH surge detection.

[0010] The predetermined day on which LH testing should be started can be indicated to the user in instructions associated with an appropriate test kit. The starting day should be sufficiently in advance of a likely ovulation day in a typical cycle, to provide a reasonable "safe" period during initial use of the method of the invention.

[0011] Preferably, at least during an initial usage cycle, commencement of testing is begun not more than 8 days, more preferably not more than 7 days, following the onset of menses.

[0012] Preferably, at least during an initial usage cycle, avoidance of unprotected intercourse is begun not more than 8 days, more preferably not more than 7 days, following the onset of menses.

45 [0013] The invention also provides a test kit for providing awareness of the status of the human ovulation cycle, comprising a plurality of disposable urinary LH concentration testing devices together with means enabling a user to record the results of frequent (eg. daily) urinary LH tests and to alert the user to the likelihood of conception occurring, characterised in that the recording/alerting means (and/or instructions associated therewith) advises the user to commence testing on a predetermined day in the time interval from numerical day 5 to numerical day inclusive 15 following the onset of menses and to abstain after the predetermined day from unprotected intercourse until at least 2 days have elapsed following the day of detection of the LH surge.

[0014] Preferably, the recording/alerting means (and/or instructions associated therewith) advises the user to commence testing in the subsequent cycle on a numerical day that is at least 4 but not more than 8 days in advance of the numerical day corresponding to the day of detected LH surge in the current cycle. Preferably, the user is advised to abstain from unprotected intercourse until at least 3 days have elapsed following the detection of the LH surge.

55 [0015] The recording/alerting means can, for example, be a chart on which the user enters the results of the daily testing, commencing on a predetermined day following the onset of menses. If desired, the chart can be provided with a slidable overlay or cursor indicating an appropriate time interval in accordance with the invention, incorporating for

example a marker that the user can locate adjacent on an identified day of LH surge and which can then indicate the end of the "unsafe" interval. As a preferred feature, the cursor can enable the user to adapt the method of the invention to modify and preferably reduce the number of test days in the subsequent cycle. This can be achieved if the cursor accommodates means to advise the user of an optimum test starting day to be used in the subsequent cycle in advance of the expected day of LH surge detection. In order to provide an adequate "safe" interval and to accommodate normal variations that are likely to occur between one cycle and another in the same individual, the revised test starting day should be set as a defined number of days in advance of the day of observed LH surge in the current cycle.

[0016] Preferably, the recording chart on which daily urinary LH concentrations can be recorded during the course of an ovulation cycle is provided with a cursor that can highlight a group of consecutive "days" on the chart and which cursor, by alignment with a "day" on which the LH surge detection is recorded, can advise the user of the residual unsafe period during the current cycle. More preferably, the cursor can advise the user to commence urinary LH concentration testing on a predetermined numerical day in the subsequent cycle during the interval of at least 4 but not more than 8 days inclusive in advance of the numerical day of LH surge detection in the current cycle.

[0017] The chart can be made re-useable, but preferably is disposable and a new chart is supplied with a plurality of assay devices sufficient for testing during a single cycle.

[0018] Alternatively, the recording/alerting means can be an electronic device, such as an electronic monitor, e.g. a micro-processor controlled device, into which the daily test results are entered, e.g. by means of an automatic reader of a sampling device, and which can calculate the calendar for the user.

[0019] Another aspect of the invention is a disposable urinary LH concentration testing advice when used as part of a test kit as defined above, comprising a reagent-impregnated immunochromatographic assay strip incorporating an anti-LH antibody labelled with a particulate direct label, such as a dye sol, gold sol, or coloured latex particles, the device having a urinary LH concentration sensitivity sufficient to provide to the user a clear test result indicative of the onset of the LH surge. Preferably the assay sensitivity is such that a clear indication is given to the user when the urinary LH concentration rises to a level in the range 20-30 mIU/ml. Suitable testing devices are described in detail in patent specifications GB-A-2204398 and EP-A-383619.

[0020] The selection of the appropriate calendar is critical to the success of the invention. If commencement of LH testing is too early, an unduly prolonged period of abstinence from unprotected intercourse will be recommended to the user and an essential objective of the invention will be negated. Following identification of the LH surge, the user should be advised promptly of the resumption of the 'safe' period.

[0021] Although there is much reported experimental work in the scientific literature on the changing urinary hormone metabolite profiles during the human ovulation cycle, we believe that the present invention constitutes the first practical use of a knowledge of the LH profile alone adapted to a simple but constructive means for alerting the user to the status of her current ovulation cycle for the primary purpose of contraception, and which is sufficiently reliable for home use. The literature does not suggest the LH measurement alone could provide sufficiently reliable contraceptive advice, especially under home-use circumstances. Rather, the thinking in the art has been that multiple factors need to be measured and correlated to provide reliable contraceptive advice, even under sophisticated laboratory circumstances.

[0022] By way of example only, practical aspects of the invention are described below with reference to the accompanying drawings.

[0023] Figures 1, 2 and 3 of the accompanying drawings illustrate assay result recording means which can be used in accordance with the invention:

Figure 1 shows a simple chart on which the result of daily LH concentration assays can be recorded.

Figure 2a shows the same chart, together with a cursor that can be run along the chart to aid the user in interpreting the results.

Figure 2b shows the cursor in place on the chart during a typical assay interpretation.

Figures 3a and 3b show a similar combination of chart and cursor as shown in Figures 2a and 2b except that the cursor of Figure 3a incorporates means to advise the user of an appropriate test starting day in the following cycle.

Figure 4 of the accompanying drawings illustrates an ovulation cycle monitoring device for use in accordance with the invention, together with an associated urine sample testing device.

Figure 5 shows the urine testing device in greater detail.

Figure 6 shows, in schematic form, the basic functions that may be required in an electronic monitor for use in accordance with the invention.

[0024] Referring to Figure 1, the chart comprises an elongated strip 100 of stout paper or similar material incorporating separate spaces for consecutive cycle days running (arbitrarily) from day 5 to day 28. Above an indication of each numerical day is a space 101 in which an assay result can be indicated by the user. Below the indication of each numerical day is a space 102 in which (if desired) the user can enter the actual date or other relevant information. Spaces A, B and C on the left hand end of the chart as illustrated, can contain instructions to the user. For the purpose of example, it can be assumed that the standard instructions to the user are to commence daily urinary LH testing on numerical day 7. The day of LH surge detection is likely to be in the interval from numerical day 12 to numerical day 20, in normal individuals.

[0025] Referring to Figure 2a, the cursor 200 comprises a simple "sandwich" structure having a front face 201 and a rear face 202 linked at the top, with a handle extension 203 by means of which the user can hold the cursor. The front face of the cursor incorporates a window 204 so that when the cursor is slipped over the chart a portion of the chart is visible through the window. Enlarged portion D of the front face of the cursor can accommodate further instructions to the user. When placed over the chart, the cursor can be slid by the user along the chart. The window is sufficient to expose four "days" of the chart at any one time. The left hand "day" is indicated by an arrow 205 on the cursor and the remaining days are identified as "1, 2 and 3".

[0026] In practice, the user should record the daily urinary LH concentration assay result on the chart in accordance with instructions associated with the assay kit, for example commencing daily LH testing on numerical day 7. On the day that the assay result indicates that the LH surge has commenced, the cursor should be moved along the chart so that the arrowed day is the present day. This will alert the user to the fact that the three immediately subsequent days (days "1, 2 and 3" on the cursor) constitute the end of the "unsafe" period and thereafter unprotected intercourse can be resumed until the next cycle.

[0027] Referring to Figure 3a, the cursor 300 accommodates a larger window 301 which exposes a total of 9 "days" of the recording chart. The sixth "day" of the cursor window is the arrowed day 302 which the user should align with the actual day of LH surge observation during the current cycle. Thereafter the cursor indicates three further days which constitute the remainder of the "unsafe" period, as described in the previous paragraph.

[0028] The five "days" revealed by the cursor in advance of the LH surge day represent a reasonable testing period for use in the subsequent cycle. A further arrow 303 on the cursor is placed below the first of these five days.

[0029] Referring to Figure 3b, it is assumed for the purposes of example that LH surge in the current cycle has been identified on day 17 of the cycle. The cursor is seen on the recording chart with the LH surge day arrow 302 adjacent the entry for day 17. The arrowed day 303 at the left hand end of the cursor window is day 12 of the current cycle. The user can assume that in her next cycle she can commence daily LH concentration testing on numerical day 12 rather than day 7 in accordance with the basic instructions with the test. The number of LH concentration tests in the subsequent cycle is therefore reduced, and unprotected intercourse need not be avoided until day 12 of the subsequent cycle.

[0030] Referring to Figure 4, the urine sample testing device comprises a flat elongate casing 400 having a locating ridge 401 on its lower surface 402. Projecting from one end of the casing is a bibulous sample receiving member 403.

[0031] The monitor comprises a casing 410 having a recess 411 in its upper surface 412 to accommodate the casing 400 of the testing device. Recess 411 incorporates a locating slot 413 into which the locating ridge 401 on the casing of the testing device can be inserted to positively locate the testing device in relation to a reading window 414 in the recess. Casing 410 contains means (not shown) such as a fluorescence reader to measure the result of a urinary LH concentration assay performed using the testing device.

[0032] The sloping front face 415 of the monitor casing incorporates a large window 416 through which information can be conveyed to the user eg. by means of an LED display or other visual output. This information can be provided in a variety of forms, such as an indication of a calender and the need to perform urine tests, and an indication of the current status of the ovulation cycle. The sloping face 415 of the casing also incorporates a button 417 which the user can press to indicate the commencement of an ovulation cycle and to start the monitor processing information relative to that cycle.

[0033] In general the monitor will be battery-powered, and incorporates in side 418 of the casing an access point such as a removable cover 419 to permit batteries to be inserted and changed.

[0034] Referring to Figure 5, the testing device is shown inverted relative to the aspect seen in Figure 1. The locating ridge 401 is now on the upper surface 500. Also in the surface 500 now uppermost is a result window 501. The body of the testing device can incorporate an immunochromatographic strip (not shown) incorporating all necessary reagents to enable an immunoassay to be formed which detects the presence and concentration of LH in a urine sample applied to the sample collecting member 403. The result of the assay can be effected by the immobilization of a labelled component, via a sandwich or competition reaction in the presence of LH in an applied urine sample, the labelled reagent becoming concentrated in a zone revealed through the result window. When the testing device is inverted and located in the recess 411 in the casing of the monitor, the result window is immediately adjacent to the reading window 414 in the monitor and the assay result can be determined. For example, if the label is a fluorescent reagent, the reading means within the monitor can detect and measure fluorescent light output from the accumulated label in the

detection zone on the strip to provide a numerically accurate concentration value for the LH in the urine sample. This information can be processed by the monitor together with calendar information resulting from the initiation of the cycle process by the user and historical data which the monitor can retain from previous cycles.

[0035] Referring to Figure 6, some of the basic elements which may be required in an electronic monitoring device are seen. The individual features can be entirely conventional, and those familiar with the art of electronics will appreciate that other combinations and arrangements of such features can be employed to achieve the objectives of the invention. For example, so-called "hard-wired" systems, and "neural networks", can be used in place of conventional microprocessors based on "chip" technology. As depicted in Figure 6, the combination essentially comprises:

[0036] A reading unit 600 to derive information from a test device, such as a test stick, the leading unit comprising an illuminator 601 and a reader 602 (represented here as a photo diode). The leading unit feeds into a conversion unit 603 to convert the optical signal into a form usable by a microprocessor 604. As an optional feature, a calibration system 605 is provided to convert the signal derived from the reading unit into data corresponding, for example, to an absolute concentration value. A timer, such as a clock 606 is required to regulate measurements within a cycle. The microprocessor 604 processes, memorizes and interprets results in the light of previous events, particularly recorded from previous cycles. The user interface 607 will generally comprise at least means, such as a push button, which the user can operate at the commencement of a cycle to initiate the operation of the device as a whole. The power supply 608 should include means, such as a memory back up capacitor 609, to prevent loss of historical data if it becomes necessary to replace batteries.

[0037] The following Examples illustrates how reliable practical contraceptive advice can be provided by means of the invention.

EXAMPLE 1

[0038] A plurality of urinary LH concentration assay devices, essentially constructed as described in Embodiment 3 and illustrated in Figures 8 to 10 of UK patent specification GB 2204398B, are used in conjunction with a recording chart as shown in Figure 1 of the accompanying drawings. In essence, each assay device comprises an immunochromatographic assay strip within a plastics casing, incorporating a mobile anti-LH antibody labelled with blue-coloured polystyrene (latex) microparticles, and having an assay result zone on the strip bearing an immobilised unlabelled anti-LH antibody capable of forming a sandwich complex in the presence of LH to provide a readily visible result in the form of a blue line appearing in a window in the casing when the LH concentration in an applied urine sample exceeds 20 mIU/ml. Daily urinary LH assays are conducted, commencing on day 7 of a human ovulation cycle (calculated as the seventh day following the onset of menses), and the day of occurrence of the LH surge is noted. Unprotected intercourse is avoided during the interval from day 7 until the third day, inclusive, following the day of occurrence of the LH surge. Conception does not occur.

EXAMPLE 2

[0039] A study was conducted with two individuals. Early morning urine samples were tested with an LH assay device as described in Example 1, and the same samples were tested in the laboratory for P3G concentration with a quantitative enzyme immunoassay. The purpose of the P3G assay was to validate the conclusions drawn from the LH positive results. Thus, a positive LH result implies that the luteal infertile phase will begin in 2-3 days time, the ovum having irreversibly passed through the uterus. If this conclusion is correct, then at least the start of a sustained rise in P3G should be detectable 3 days after the first positive LH result, as it is known that the luteal phase can be defined by the rise in blood progesterone.

[0040] The tables of results show data from 3 cycles of each volunteer. Column 1 (day of cycle) shows the day of testing, relative to the onset of menses. The first observation in each set is that obtained four days before the first positive LH result, to show the range of background (or non-elevated) P3G values, above which a rise can be detected.

[0041] The final column relates the actual results to the advice that a user would receive if employing a recording chart as illustrated in Figures 2a/b, based upon the timing of the LH positive result. LH results are simply expressed as positives or negatives, without any attempt to rank or deduce quantitative information. The first positive result is expressed in bold type, as this is taken as the key piece of information.

[0042] P3G concentrations are given for each day, but no attempt is made to define threshold values, as such values vary considerably from cycle to cycle. Cusum analysis could be used to identify the P3G rise, but in these studies, the onset of a sustained rise is clearly evident without the need for statistical treatments. For example, in cycle 1 of volunteer A, values of P3G approaching 3,500 ng/ml occur up to and including the first LH positive day. The values found on the "safe" days are all at least 60% higher than those observed before the positive LH result.

[0043] In every cycle from each volunteer there is a clear and unmistakable rise in P3G values coinciding with start of the infertile phase, as deduced from the LH results, so confirming the surprising accuracy of infertile phase prediction

EP 0 745 854 B1

from urinary LH detection.

INDIVIDUAL A

5 [0044]

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Cycle 1 (30 days)			
Day of cycle	LH result	P3G conc (ng/ml)	Cursor "day"
12	-	1435	
13	-	1666	
14	-	3222	
15	-	1012	
16	+	3369	
17	+	4510	1
18	-	3256	2
19	-	7052	3
20	-	5244	Safe
21	-	9944	Safe
22	-	9521	Safe

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Cycle 2 (28 days)			
Day of cycle	LH result	P3G conc (ng/ml)	Cursor "day"
11	-	689	
12	-	1235	
13	-	873	
14	-	2477	
15	-	2838	
16	+	3237	1
17	-	5522	2
18	-	8578	3
19	-	13309	Safe
20	-	5658	Safe
21	-	8622	Safe

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Cycle 3 (29 days)			
Day of cycle	LH result	P3G conc (ng/ml)	Cursor "day"
11	-	1714	
12	-	864	
13	-	1518	
14	-	1818	
15	+	2249	

EP 0 745 854 B1

(continued)

Cycle 3 (29 days)			
Day of cycle	LH result	P3G conc (ng/ml)	Cursor "day"
16	+	1388	1
17	-	2057	2
18	-	5404	3
19	-	6756	Safe
20	-	9147	Safe
21	-	8723	Safe

INDIVIDUAL B

[0045]

Cycle 1 (31 days)			
Day of cycle	LH result	P3G conc (ng/ml)	Cursor "day"
14	-	494	
15	-	776	
16	-	315	
17	+	540	
18	+	554	
19	-	1081	1
20	-	3498	2
21	-	2489	3
22	-	3316	Safe
23	-	6085	Safe
24	-	4562	Safe

Cycle 2 (24 days)			
Day of cycle	LH result	P3G conc (ng/ml)	Cursor "day"
12	-	1505	
13	-	1379	
14	-	615	
15	-	1567	
16	-	841	
17	-	1493	1
18	-	800	2
19	-	1785	3
20	-	5414	Safe
21	-	8053	Safe
22	-	7446	Safe

Cycle 3 (35 days)			
Day of cycle	LH result	P3G conc (ng/ml)	Cursor "day"
18	-	746	
19	-	456	
20	-	716	
21	-	500	
22	+	775	
23	+	600	1
24	-	1864	2
25	-	2618	3
26	-	3183	Safe
27	-	5601	Safe
28	-	7327	Safe

Claims

1. An electronic monitoring device programmed for monitoring the ovulation cycle in an individual human subject, comprising means (417, 607) for initiating the monitoring of a cycle, means (414, 600) for recording the urinary concentration of luteinizing hormone (LH), in conjunction with one or more urine testing devices (400) readable by the monitoring device, means (603, 604) for calculating a testing commencement day in a current cycle based on recorded measured LH concentrations obtained during one or more previous cycles in the same individual subject, said calculated testing commencement day being in the interval from numerical day 5 to numerical day 15 inclusive following the onset of menses, and display means (416).
2. A device according to claim 1, wherein said testing commencement day is a numerical day in the current cycle that is at least 4 but not more than 8 days in advance of the numerical day corresponding to the day of detected LH surge in the previous cycle.
3. A device according to claim 1 or claim 2, wherein the display means advises the user to commence testing on the calculated testing commencement day and indicates the current status of the cycle.

Patentansprüche

1. Elektronische Überwachungs Vorrichtung, die zum Überwachen des Ovulationszyklus einer menschlichen Person programmiert ist, aufweisend Mittel (417, 607) zum Starten des Überwachens eines Zyklus, Mittel (414, 600) zum Aufzeichnen der Konzentration des luteinisierenden Hormons (LH) im Urin zusammen mit einer oder mehreren Urin testvorrichtungen (400), die von der Überwachungs Vorrichtung auslesbar sind, Mittel (603, 604) zum Errechnen eines Teststarttages in einem laufenden Zyklus, basierend auf den aufgezeichneten, gemessenen LH-Konzentrationen, die während eines oder mehrerer vorheriger Zyklen derselben Person erhalten wurden, wobei der errechnete Tag des Testbeginns im Intervall vom zahlenmäßig 5. bis zum zahlenmäßig 15. Tag einschließlich, der auf den Beginn der Menstruation folgt, liegt, und Anzeigemittel (416).
2. Vorrichtung nach Anspruch 1, dadurch gekennzeichnet, dass der Anfangstag des Testens ein zahlenmäßiger Tag im laufenden Zyklus ist, der mindestens 4, jedoch nicht mehr als 8, Tage vor dem zahlenmäßigen Tag liegt, der dem Tag des detektierten LH-Anstiegs im vorherigen Zyklus entspricht.
3. Vorrichtung nach Anspruch 1 oder 2, dadurch gekennzeichnet, dass das Anzeigemittel der Benutzerin rät, das Testen am errechneten Anfangstag des Testens zu beginnen, und den gegenwärtigen Stand des Zyklus anzeigt.

Revendications

1. Dispositif de surveillance électronique programmé pour surveiller le cycle d'ovulation chez un sujet humain individuel comprenant un moyen (417, 607) pour initier la surveillance d'un cycle, un moyen (414, 600) pour enregistrer la concentration urinaire de l'hormone lutéinisante (LH) en liaison avec au moins un dispositif d'analyse protocolaire à des fins de test d'urine (400) pouvant être lu par le dispositif de surveillance, un moyen (603, 604) pour calculer un jour de début d'analyse de contrôle dans un cycle courant basé sur les concentrations de LH mesurées enregistrées obtenues pendant au moins un cycle précédent chez le même sujet individuel, ledit jour de début d'analyse protocolaire à des fins de test calculé étant compris dans l'intervalle du jour numérique 5 au jour numérique 15 inclusivement suivant le début des menstruations, et un moyen d'affichage (416).
2. Dispositif selon la revendication 1, dans lequel ledit jour de début d'analyse de contrôle est un jour numérique dans le cycle courant qui est au moins 4, mais pas plus de 8 jours, en avance sur le jour numérique correspondant au jour de la poussée de LH détectée lors du cycle précédent.
3. Dispositif selon la revendication 1 ou 2, dans lequel le moyen d'affichage recommande à l'utilisatrice de commencer l'analyse protocolaire à des fins de test le jour du commencement de l'analyse protocolaire à des fins de test calculé et indique l'état courant du cycle.

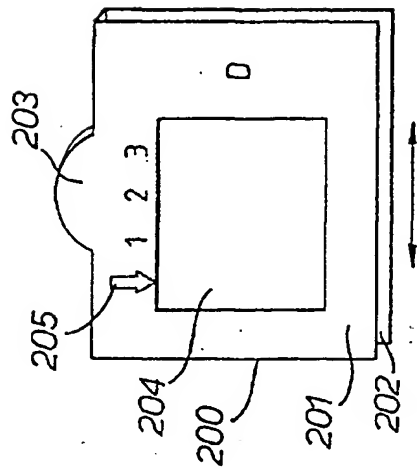
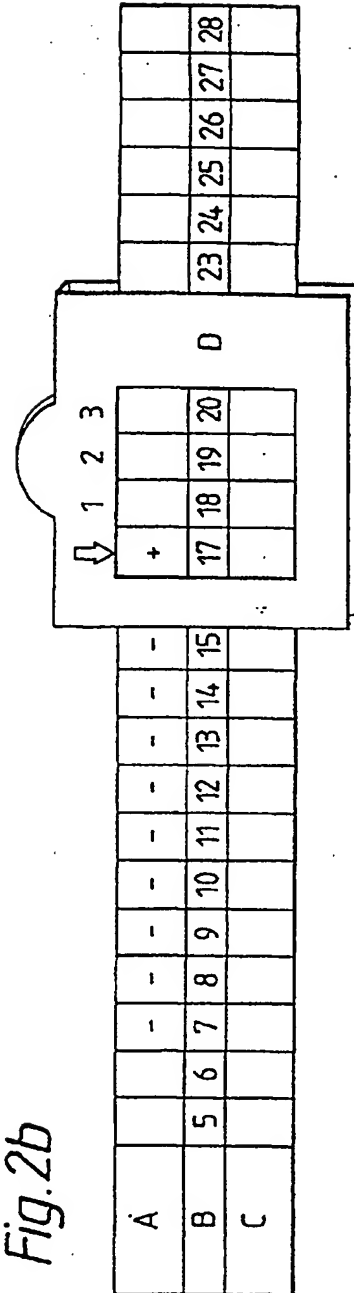
Fig. 1.

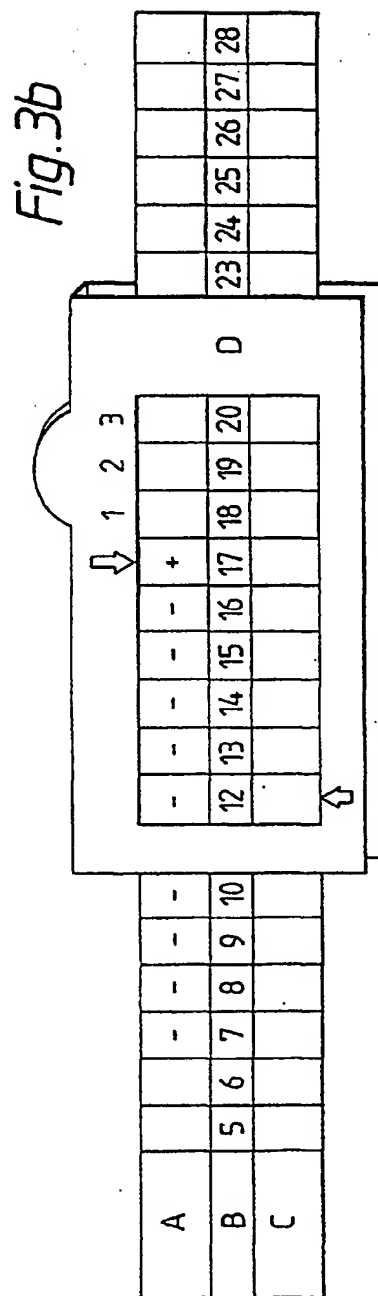
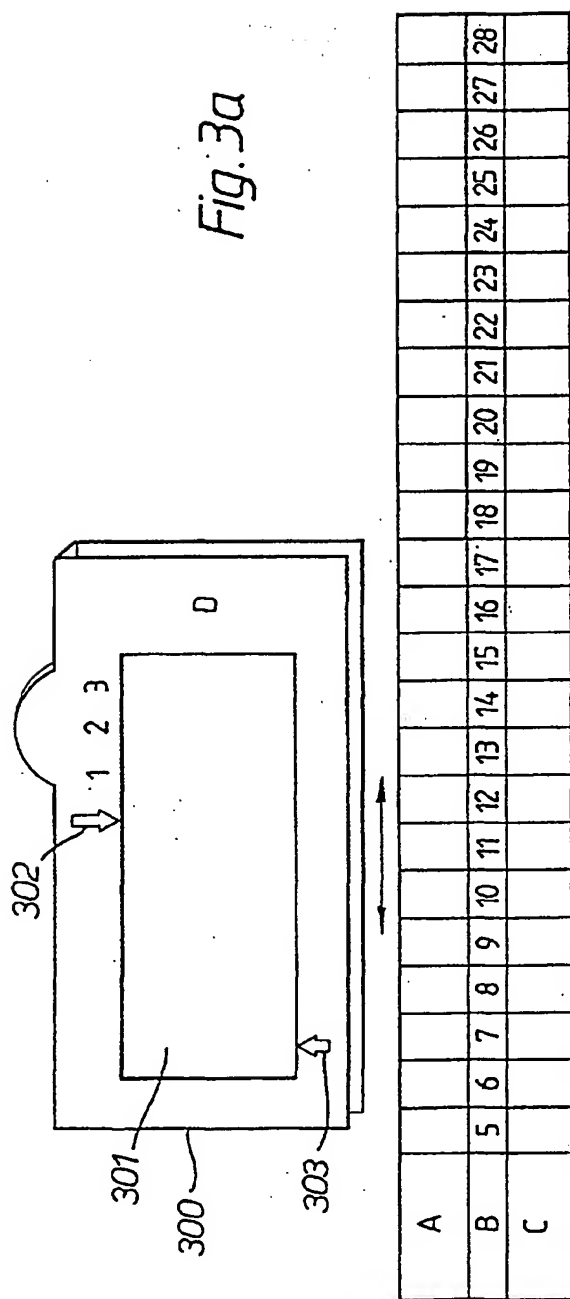
A																													
B	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28					
C																													

101

102

100

[illegible][illegible]



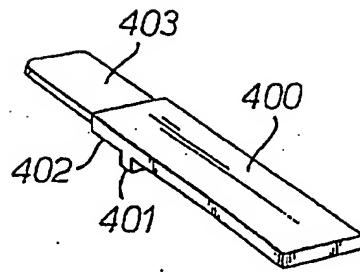


Fig. 4.

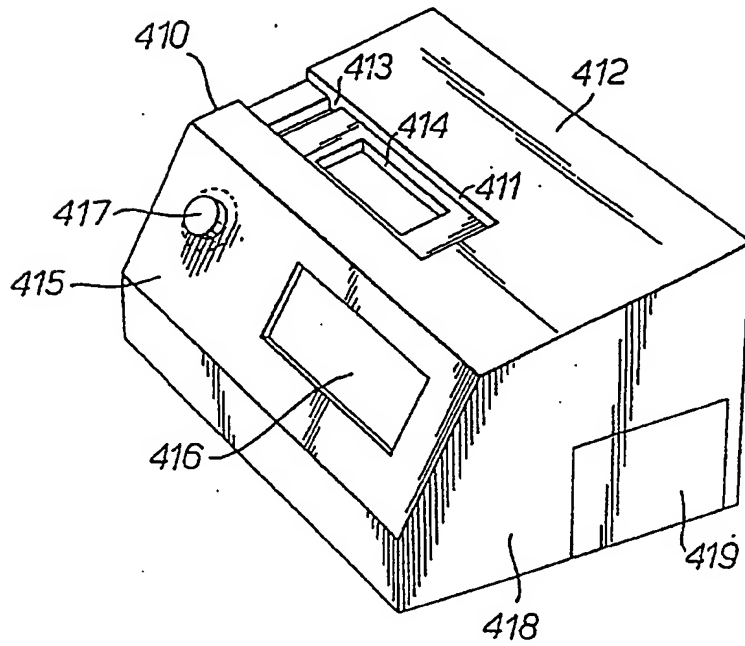


Fig. 5.

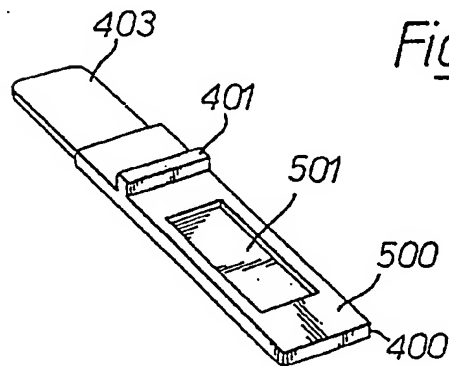


Fig. 6.

